OBJECTIVES: To compare trials of the four anti-epileptic drugs (AEDs) approved specifically for the adjunctive treatment of primary generalized tonic-clonic seizures (PGTCS): topiramate [TPM] (1999), lamotrigine [LTG] (2006), levetiracetam [LEV] (2007), lamotrigine-XR [LTG-XR] (2010), and perampanel [PER] (2015). **METHODS:** Trial data were identified through a systematic literature review. Main inclusion criteria: randomized, controlled, PGTCS with or without other generalized seizure types, and published 1989-2014. Key exclusion criteria: predominantly children/adolescents and intravenous drug study. Data were abstracted from indexed publications, clinicaltrials.gov, and regulatory reports of the United States Food and Drug Administration and European Medicines Agency. **RESULTS:** Five PGTCS trials [TPM-RCT (n=80), LTG-RCT (n=117), LEV-RCT (n=164), LTG-XR-RCT (n=146), PER-RCT (n=163)] were identified. All trials were placebo-controlled where baseline AEDs were continued into the trial and consisted of the standard of care (SOC) at the time. Trial designs were similar with minor exceptions: PER-RCT allowed 1-3 baseline AEDs (others 1-2), LEV-RCT and PER-RCT had shorter titration periods (4 versus 7 & 8 weeks), and LEV-RCT had the longest maintenance period (20 versus 12 & 13 weeks). Baseline PGTCS frequency was similar between trials except TPM-RCT which was higher (4.5-5.0 versus 2.3-3.0 per 28 days). The presence of LTG, LEV, and zonisamide in the SOC increased over time while the use of carbamazepine, phenytoin, and phenobarbital decreased. Valproate and TPM use fluctuated but appeared stable. In the latest phase III trial, PER-RCT had the following SOC composition, 43% valproate, 39% LTG, 15% TPM, 31% LEV, 12% zonisamide, 8% carbamazepine, 6% phenytoin, and 4% phenobarbital. **CONCLUSIONS:** Our review indicates that while the trial designs have remained similar over time, the SOC has evolved with the approval of new PGTCS medications. The latest trial, PER-RCT, has an SOC that is comprised heavily of the most recently approved PGTCS drugs.

PRM229

DO WE NEED TO STRENGTHEN STUDY DESIGN IN OBSERVATIONAL STUDIES?

Longagnani C, Simoni L, Fiori GG
Medineos Observational Research, Modena, Italy

OBJECTIVES: Guidance and standards are made available by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) as reference tools for methodology and transparency of post-authorization studies. They are cited by the Guideline on good pharmacovigilance practices (GVP) Module VIII as relevant scientific guidances. Here we report an analysis conducted on Pharmacovigilance Risk Assessment Committee (PRAC) minutes regarding methodological issues. **METHODS:** All publicly available minutes of PRAC meetings from July 2012 to March 2015 were considered. The number of submitted post-authorization safety study (PASS) protocols requiring endorsement was recorded (excluding advices), as well as endorsement/ refusal and reason. ENCePP documentation was consulted. **RESULTS:** From July 2012 to March 2015, 33 PASS protocols submitted to PRAC requiring endorsement were considered, increasing with years: 2 in 2012, 8 (17 considering resubmissions) in 2013, 18 (24 considering resubmissions) in 2014. The total number of evaluations was 54. Thirteen were endorsed at the first step (including endorsement with changes requested), while 20 required at least one amendment reaching approval up to 15 months after submission. The most common reasons for refusal concerned study design (20 cases), mainly reporting designs not allowing to fulfil study objectives (N=14). Furthermore, PRAC review asked for alternatives to reduce bias and confounding (N=2), simplifications aiming at reinforcing the observational nature of the study (N=1), further justification of sample size (N=1) and considerations on feasibility (N=1). From 2013 to 2014 an increasing number of endorsed PASS protocols was observed (7/17 and 12/24 respectively). During the same years ENCePP Checklist for Study Protocols and ENCePP Guide on Methodological Standards in Pharmacoepidemiology were reviewed, and the number of studies included in the ENCePP e-register increased. **CONCLUSIONS:** An increasing use of guidance and standards will allow strengthening robustness of design and results of observational studies.

PRM230

ECONOMIC STUDY DESIGN FOR THE OPTIMIZE STUDY ON ORBITAL ATHERECTOMY AND DRUG-COATED BALLOON DEVICES FOR THE TREATMENT OF BELOW-THE-KNEE PERIPHERAL ARTERIAL DISEASE

Martinsen BJ[1], Weber SA[2], Pietzsch ML[2], Behrens A[1], Weatherspoon M[1], Igyarto Z[1], Zhao R[3], Kotlarz H[1], Pietzsch JB[4]
[1]*Cardiovascular Systems, Inc., St. Paul, MN, USA,* [2]*Cellogic GmbH, Berlin, Germany,* [3]*University of Minnesota, Minneapolis, MN, USA,* [4]*Wing Tech Inc., Irvine, CA, USA*

OBJECTIVES: Present the economic study design of the OPTIMIZE study on orbital atherectomy system (OAS) and drug-coated balloon (DCB) treatment of peripheral artery disease (PAD) patients. Treating patients with calcified peripheral arterial lesions can be challenging and costly. The impact of OAS and DCBs in treating calcified lesions has been studied independently. The objective of this study design is to assess the economic impact of treating below-the-knee (BTK) calcified PAD lesions with OAS+DCB compared to treating BTK calcified lesions with DCB alone (without OAS). **METHODS:** This prospective, multi-center, post-market pilot study comparing OAS with adjunctive DCB angioplasty versus DCB angioplasty alone for treatment of calcified BTK lesions is a 1:1 randomized controlled study of 50 patients with calcification. In addition to clinical outcomes, health economic outcomes will be collected for the index procedure as well as additional procedures required during the clinical follow-up period. **RESULTS:** Health economic outcomes will be measured at the index procedure, at 30 days, 3 months, 6 months, 12 months, and 24 months post procedure for the treatment of PAD and its complications (repeat procedures, amputations, etc.). Health-related quality of life will be measured using the EQ-5D instrument. Resource utilization will be collected from case report forms and hospital accounting systems, using site-specific procedure code information of relevant OPS (German sites), CHOP (Swiss sites), and MEL codes (Austrian sites). Analyses from the third-party payer perspective will be informed by country-specific reimbursement amounts, using Germany as the initial reference case. Resulting cost difference and incremental cost-effectiveness are the main economic outcomes targeted in this analysis. **CONCLUSIONS:** Prospective inclusion of health-economic endpoints in clinical trials for PAD is important to support future decision-making by payers and providers. The OPTIMIZE study collects targeted information on quality of life and resource utilization to facilitate future health-economic analyses.

PRM232

METHODOLOGICAL CONSIDERATIONS FOR THE IMPLEMENTATION OF A EUROPEAN MANDATED RETROSPECTIVE DRUG UTILISATION STUDY (DUS) TO INVESTIGATE THE USE OF DEXMEDETOMIDINE (DEXDOR®) IN CLINICAL PRACTICE

Stein D[1], Weatherall M[2], Garratt C[2], Aantaa R[3], Conti G[4], Lewis MA[5], Moore N[6], Gutthann S[7]
[1]*UBC: An Express Scripts Company, Dorval, QC, Canada,* [2]*Orion Corporation Orion Pharma, Nottingham, UK,* [3]*University of Turku, Turku, Finland,* [4]*Catholic University Institution of Anaesthesiology, Rome, Italy,* [5]*EPES Epidemiology GmbH, Berlin, Germany,* [6]*University of Bordeaux, CHU de Bordeaux, Hospital Pellegrin, Bordeaux, France,* [7]*RTI Health Solutions, Barcelona, Spain*

OBJECTIVES: Dexmedetomidine was approved for ICU sedation in adults in the EU in 2011, but has been available in other countries since 1999 and used in many different clinical situations including in children. This study evaluated off-label use of dexmedetomidine in usual care in the EU. **METHODS:** A chart review DUS of patients treated with dexmedetomidine was conducted in 16 hospitals across Austria, Finland, Germany and Poland. Patients were identified either prospectively or retrospectively, with anonymised data abstraction performed retrospectively post-administration. Chart data on patient demographics, indication, dexmedetomidine administration, concomitant medications and therapeutic effectiveness were collected via an electronic data collection tool. **RESULTS:** 2,000 patients received 2,159 administrations of which 36.6% contained elements not according to the SmPC. Collecting off-label use was a concern to some sites and ethics committees, resulting in high site attrition and relatively slow start-up. Collecting sufficient mature dexmedetomidine use early after launch required focus on prolific users, while excluding regions where dexmedetomidine uptake was slow. Site selection was performed blinded by the Steering Committee to avoid bias. The study required collaboration across many hospital departments. Varied medical records systems required site-specific approaches to patient identification; some sites performing database searches, others using a manual process. Restricted access to records of patients from other hospital departments in some cases necessitated completion of paper worksheets by non-study hospital staff. Anonymised data collection avoided the need for informed consent but precluded patient verification and data queries, thus robust electronic data checks were essential. Data were regularly reviewed for evidence of duplication of patients within sites. **CONCLUSIONS:** Chart review DUS was successful in investigating off-label dexmedetomidine prescribing. Study conduct flexibility was essential to meet different needs of study sites and ensure study success. Close attention to potential sources of bias was required to ensure a robust outcome.

PRM233

TRIAL DESIGN AND MARKET ACCESS IMPLICATIONS: OUTCOMES FROM COMPARATOR CHOICE

Khoury C[1], Duque R[1], Freiberg M[2]
[1]*Quintiles Consulting, Neu-Isenburg, Germany,* [2]*Quintiles Commercial, Mannheim, Germany*

OBJECTIVES: The choice of comparator drug is a critical factor in successful market access, pricing and reimbursement by national payer bodies. Varying requirements specified for the comparator selected have led to approaches that differ by country. Legislation introduced in Germany in particular has affected studies in progress. As HTA agencies differ per country, the objective of the analysis which covers Germany, UK and France is twofold: - Do market access regulations influence trial design? - Do the chosen trial designs cover national pricing and reimbursement regulations? **METHODS:** Published benefit assessments from selected HTA agencies websites such as G-BA, NICE and HAS were used to analyze diabetes drug assessments in terms of requested comparators and final recommendation. Furthermore, Clincialtrials.gov was used to analyze the trials in diabetes and their design. **RESULTS:** Of the 49 HTA assessments by G-BA, HAS and NICE analyzed, 10 assessments (20%) had an inappropriate comparator chosen. This resulted in eight negative recommendations, one positive with restrictions and one positive recommendation. Most of the HTA assessments with a positive outcome presented head-to-head or adjusted indirect comparisons. Unadjusted indirect comparisons were mainly rejected; and a mixed approach was allowed in France and England but not recommended in Germany. **CONCLUSIONS:** Having solely marketing authorization (EMA) in mind when designing a trial can lead to an unsuccessful drug launch with regards to national pricing and reimbursement decisions. More specifically, the choice of comparator is considered as the most important factor for benefit assessment in Germany and the methodology applied is crucial to obtaining a positive outcome. In France and England, the use of specific guidelines for the choice of comparators and comparison methodology developed by NICE and validated by the HAS, is particularly relevant to obtain a positive outcome.

PRM234

THE DIABETES TELEPHONE STUDY: DESIGN AND CHALLENGES OF A PRAGMATIC CLUSTER RANDOMIZED TRIAL TO IMPROVE DIABETIC PERIPHERAL NEUROPATHY TREATMENT

Adams AS[1], Bayliss E[2], Schmittdiel JA[1], Altschuler A[1], Dyer W[1], Neugebauer R[1], Jaffe M[3], Young JD[4], Kim E[4], Grant RW[1]
[1]*Kaiser Permanente Division of Research, Oakland, CA, USA,* [2]*Kaiser Permanente, Denver, CA, USA,* [3]*Kaiser Permanente South San Francisco Medical Center, South San Francisco, CA, USA,* [4]*Kaiser Permanente Oakland Medical Center, Oakland, CA, USA*

OBJECTIVES: Management of symptomatic diabetic peripheral neuropathy (DPN) is complicated by a lack of evidence regarding the comparative effectiveness of available agents, frequent side effects, and the need for ongoing symptom assess-